An Oration
ON
THE USE OF FOXGLOVE AT THE BEDSIDE.*

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THE kind invitation to address this distinguished assembly I deem a very great honour. It was unexpected, and at first I even felt a little surprised, having been in close relationship neither with Birmingham nor with the General Hospital and its physicians. But one name appeared in your letter which gave a key to why this great honour might have been bestowed upon me. The name of the discoverer of the wonderful qualities of the foxglove, William Withering, doubled the honour of the invitation, the pleasure of accepting it, and, at the same time, gave me an imperative and welcome hint as to the most suitable subject to offer for my lecture.

Digitalis is one of the most famous drugs in our pharmacopoeia; it interests the profession profoundly, even more than many of the most modern forms of treatment. Articles of every size and in every tongue, written for practical use, or of a more or less purely scientific character, fill the medical weeklies and the big archives all over the world. When by superficial judges, sometimes even among medical men, drug treatment and internal medicine are estimated as of no real value, often to be stupid and dangerous, the effects of digitalis treatment supply us with the most impressive and convincing arguments to silence the ignorant. Administered at the right moment, in the right case, and in adequate form, it may work little short of a miracle. Not only the commencing young doctor, but also the older and experienced physician, is surprised by its continued success.

Those who organized this meeting approved my wish to speak exclusively on the practical problems of digitalis, and not on the numerous experimental investigations of its action on heart muscle and vessels. I have good and sound reasons for this restriction. With his growing experience the older physician learns by and by how much individual treatment is necessary in nearly every case. Withering met with the same experience, developing his methods only in the course of many years. "Scientific" evidence and reasoning, often only superficially accurate, cannot yet be accounted the final argument for or against the administration of digitalis in a special case. The dose and form of treatment have to be determined by the real benefit the patient derives from it. What helps the individual patient most is to be taken as the best treatment for him, whether it be possible or not to analyse its action in every detail. It is the old question of the abstract science of medicine on the one side, and the practical art of healing on the other—or, in more popular form, of the old saying about the pudding and its proof.

I will now try to answer some of the more important questions concerning digitalis treatment. I do not in any way intend to put my words before you as final arguments. I personally do not regard them as such; my views were born and grew up at the bedside, and are still developing. Every day brings new facts, and from these ever-growing personal experiences I will try to tell something perhaps interesting to my medical listeners.

INDICATION.

Digitalis is indicated in all cases of heart failure—that is, where insufficient functioning of the heart is the cause of the pathological condition. This holds good irrespective of the cause of the heart failure itself. On these two points I fully agree with Eggleston's[1] conclusions. I even used part of this author's words. It must be realized, however, that these conclusions are very far from being generally accepted. In all countries I know, and in the majority of textbooks, important exceptions are still brought forward. In arterial hypertension, aortic valvular disease and aortitis, as well as in cases with a marked slow pulse, there is a strong belief that digitalis should never be given—a belief highly detrimental to the patient.

Nearly twenty years ago I had the honour of speaking to the British Medical Association at its meeting in London on the subject of digitalis.[2] The purpose was to establish a parallel between experimental and clinical evidence of its action on the heart. My final words were at that time, "Give digitalis a fair trial in every case"; and "if ever I should acquire a reputation for treating heart patients with success it will be from giving digitalis in cases where authorities and textbooks forbid it." After my sometimes even dramatic experiences during the two last decades I am still, and even more strongly, of the same opinion.

DOSAGE.

The difficulties of exact and correct dosage of digitalis are well known and greatly lamented by nearly every author. Complaints about the lack of knowledge of the exact content of active substance in our digitalis drugs are abundant, especially so in the hundreds of pamphlets about new and ever-better preparations of digitalis thrown on the market. Every new product is recommended as giving the best opportunity for exact dosage, which is looked upon as the one and principal condition for correct treatment. I never felt this lack of knowledge as a real difficulty, but daily observation is absolutely essential in every case to decide how much should be given, and how long the treatment should be continued. The most perfect dosage instructions will not absolve us from this imperative command and from our serious responsibility. I do not in the least despise or deny the great value of exact work at the bedside, and lack of exact knowledge of the active value of a special digitalis drug need never hamper us in deciding between larger or smaller doses.

Following the old custom I have made use of large, medium, and small doses, a distinction which needs no special explanation and is easily followed at the bedside. The only requirement is to adopt a certain unit of activity which may be the basis of our dosage. For such a unit it seems easier to select small doses, which can be given singly or multiplied to any extent, rather than to adopt larger doses to be divided into smaller portions.

What quantity of which digitalis preparation should be chosen as a unit?

THE BEST FORM IN WHICH DIGITALIS SHOULD BE GIVEN.

As many chemical factories exist, so many different preparations of digitalis are produced, under most promising names and with the strongest recommendations. By this ever-increasing number of products and names our choice becomes more difficult every day, and a really dangerous state of affairs results. Digitalis treatment is one of the most important and serious duties of the general physician; it demands a great deal of skill, power of observation, keen interest, and experience. A long life is too short to learn enough about this wonderful drug. To make use of all those preparations would complicate further our already numerous difficulties, and would necessitate as many subdivisions of experience as there are different preparations. It is for this reason that I have been led to restrict as far as possible the number of preparations given; as a matter of fact there is, at the end, only one form with which I have become really familiar. It is the standardized (or titrated) powder of dried leaves, obtained as far as possible from the same reliable source. Experience has driven me back to the leaves every time I had been led astray and made regular use of any other preparation. As to the unit required, a simple logical argument helped me. All modern digitalis derivatives are, or are said to be, standardized to one decigram of the powdered leaves; then why should I not take this quantity of leaves itself as my unit?

It may be that even the standardized leaves are variable in their composition; nevertheless they may be looked upon as containing all the active substances with which Nature endowed this exceptionally important plant. On the other

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hand, most digitalis preparations contain only part of the substances. As a matter of fact, this can be used to advantage. A long time ago I had many pleasant and interesting discussions with your lamented pharmacologist Arthur Cushny, perhaps the very best connoisseur of digitalis, as to whether it might be feasible to separate the different active substances of digitalis and to put them together again in various combinations. This would make it possible to avoid such factors as were undesirable in certain cases—for instance, the vagus influence causing slow pulse or disturbance of conductivity, the constrictor influence in high blood pressure, and so on. But this plan has not yet materialized, and it seems very improbable that it will be established in the near future. Even so, it would prove extremely difficult to select those cases in which such special combinations should be used. At present I believe it to be better tactics to give digitalis with full active power and to combine it with such substances as may counteract undesirable influences. I shall have to deal with such adjuvants a little later. Therefore in the present state of knowledge I prefer to use the original foxglove in the form of titrated powdered leaves as my basis for digitalis treatment, and to administer special preparations for generally recognized special purposes only.

Such a special purpose is the immediate effect required in an emergency; here subcutaneous and intravenous injections of certain digitalis derivatives are of the greatest use. This form of treatment, initiated by Albert Fraenkel, has in the course of time developed greatly, and is now a valuable and generally accepted means for treatment, not only in urgent cases, but also where the stomach absolutely refuses to retain the drug, or where the onflow of the blood to the heart is slowed so much by abdominal stasis that the effect of administration by the mouth is too greatly delayed and diminished.

Not only are digitalis derivatives used for intravenous injections; the pure active substances of strophanthus—strophanthine and ouabain—have come into use. This form of treatment is impossible without a most exact dosage. Its effects are instantaneous, which makes such exactness possible.

Rectal administration in the form of microclysters, or in suppositories, is very helpful in the same category of cases where oral administration is impossible.

Adjuvants in Digitalis Treatment.

I have previously mentioned the combination with digitalis of such active substances as might alter the action of digitalis in some direction. One such adjuvant is atropine, which may be expected to lessen the stimulating influence on the vagus—one of the most powerful functions of the foxglove. It is indicated, or is at least rational, in cases of marked bradycardia of different origins, and where disturbance of conductivity is present or is to be feared. It should be given under careful observation, and should not be pushed on theoretical reasoning only. Caffeine may also be named in this connexion, in so far as it may help in combating further increase of bradycardia.

Diuretics have a greatly appreciated value in digitalis treatment. Caffeine and the various forms of theobromine render invaluable services. Among the most active of these substances euphyllin, in suppositories or intravenously injected, is now generally used in German-speaking countries, and with increasing success.

The new valuable mercury preparations novasurol and salyrgan have been introduced by Paul Saxl, one of the assistants at the First Medical Clinic in Vienna. Careful use of these injections at the right moment and in the proper dosage constitutes perhaps the greatest recent progress in the treatment of heart patients. The resulting depletion of the body relieves the overfilled circulation, lessens the circulatory resistance, and frees the heart and kidneys from a great part of their task, so that it smooths the way for better action by the foxglove.

Diet, of course, is an indispensable adjuvant in dropsical cases; it is so well known that I will not dwell upon this subject.

Venesection is generally accepted as one of the most beneficial factors in plethoric arterial hypertension and in extreme stasis of the lungs or liver. It is important to withdraw blood immediately before the beginning of digitalis treatment; this often permits the use of large doses of digitalis which might seem dangerous otherwise. Multiple tapping of the dropsical limbs may have the same effect, and in long-standing cases may be the only means left of freeing the body of its burden. Nevertheless, it is doubtless a great advantage that the above-mentioned novasurol and salyrgan make it possible to avoid venesection and tapping in most cases.

Adjuvants Regulating the Heart Rhythm.

From the very beginning of the studies on cardiac arrhythmia, which over thirty years ago opened a new chapter of cardiology, James Mackenzie and I contended that most arrhythmias were not signs of heart failure, as had been generally believed up to that time. On the contrary, by disturbing the pumping mechanism of the heart, they must be looked upon as a most serious cause of insufficient heart function and consequent circulatory trouble. This now generally acknowledged, but not yet consequently applied opinion, made me feel the urgent need for forms of treatment which would abolish irregularities and restore the normal mechanism of the heart. At a loss for theoretical and experimental suggestions, I had to try what sort of drugs might help. Digitalis itself, which in large doses may be the cause of regular extra-systoles, may in very small doses abolish this phenomenon and be very helpful in combating auricular fibrillation. The "nervines," bromides, valerian, camphor, and other sedatives, gave unsatisfactory or only temporary results.

Strychnine, from olden times given in your country for routine heart treatment, was my first success. A good friend of mine, not yet 50 years of age, dying slowly from aortic incompetence, never complaining but having a terrific Corrigan pulse, felt extremely miserable as soon as the periods of extra-systolic beats occurred. He suffered badly under the gigantic "post-compensatory" pulse waves, and one day told me very clearly that as an old friend and a professor of medicine I ought to be ashamed of not being able to free him from this unbearable trouble. Thus stimulated to further experiments, I tried strychnine also; two milligrams a day at once abolished the extra-systoles, and every time his arrhythmia returned the drug proved faithfully effective to the end. After this truly experimental evidence I have been giving strychnine in hundreds of cases. It helps, but not always sufficiently, and seems to lose its influence after a certain lapse of time. Later, after becoming aware of the marvellous action of quinine, I prescribed strychnine in combination with this drug, and with immediate and lasting success; it is still my favourite combination in cases of extra-systolic irregularities without marked heart failure.

Quinine is the greatest regulator of the arrhythmias of extra-systolic character, including auricular fibrillation, though in many cases quinidine has a stronger action. It is unnecessary to dwell upon quinine therapy,[3] which has found its way all over the world, and I may limit myself now to the combination of quinine and digitalis.

This combination seems to be a very old one—at least, it was very popular in the second half of the last century, and quinine had a reputation as a heart drug little short of the foxglove,[4] but I did not know this. During my search for heart-regulating drugs I carefully excluded quinine from my efforts, having seen from the experimental work of Stokvis and of Santesson that it is a heart-paralysing poison. On asking a well-known older clinician why under such conditions he treated his heart patients with digitalis *plus* quinine, he said, "Because my patients and myself are, in the long run, equally satisfied by this combination." That this seemingly unwise saying contained a great deal of wisdom I realized the moment a patient told me, and demonstrated, that he was able to stop his paroxysmal auricular fibrillation with the help of one gram of quinine. Since that time I have prescribed the combination of quinine and digitalis in the great majority of my heart cases, not only where arrhythmia is present, but also where large doses of digitalis seemed urgently needed and where

concomitant disturbance made quinine desirable. Shortly after the war, when quinidine treatment for abolishing auricular fibrillation became known among the English-speaking profession, it was said, but on theoretical arguments only, that this combination must be avoided. As far as my information goes, this not justified opinion is now generally abandoned.

Vasomotor Adjuvants.

Vasomotor drugs are desirable in hypotonic cases for increasing the tone of widened peripheral vessels, and conversely in hypertonic heart cases to counteract the vasotonic influence of digitalis. The vaso-constrictor strychnine seems indicated in the first instance, and apparently fulfils this task to a certain extent. The second indication is of far greater importance, especially when we take into account that high blood pressure has been a very strong contraindication against digitalis. In this connexion it would be interesting to know whether Withering's cases, in which, as he phrased it, "the fibre is tense," are comparable with our patients with arterial hypertension of to-day. The two adjuvants that had the best effect in my hands are papaverine and quinine, mostly given together. Both have a marked dilator action on the peripheral circulation. In the case of quinine, vaso-dilatation and fall of blood pressure are a regular event after intravenous injection, as well as in the treatment of malaria and in attacks of paroxysmal tachycardia, in which it nearly always stops the paroxysm instantaneously. Therefore it is quite reasonable to add these two substances to our digitalis doses in all cases where a constricting action of digitalis on the arteries should be avoided. The wonderful vaso-dilator action of the nitrites is of such short duration that it is not very helpful in chronic treatment. Theobromine should not be omitted from our list; it is given alternately with digitalis with fairly good success.

The practical issue of what I have been relating here very superficially is that I make a regular use of the quinine-digitalis combination, adding strychnine in hypotonic cases, especially when it seems desirable to counteract the depressing action of quinine, conversely adding papaverine in hypertonic cases. Apart from the logical reasoning and experimental evidence that may underlie this form of treatment, I may repeat the words of that already quoted old colleague, that "my patients and myself and the many physicians who adopted this method are quite satisfied with its results in cases where strong digitalis treatment otherwise might seem more or less risky."

PROLONGED DIGITALIS ADMINISTRATION.

In speaking about this very important problem it will be necessary to distinguish between prolonged treatment (1) with very small doses, and (2) with larger doses.

1. *Treatment with Very Small Doses.*

Rather contradictory opinions exist about the usefulness, or the complete inactivity, of very small doses of digitalis. Experimental work on the normal dog's heart cannot help us. At the bedside we are treating diseased hearts, where the different functions may be reduced or exaggerated in an endless number of grades, combinations, and varieties. Very small doses may, theoretically, have a distinct influence in certain functional disturbances which is not manifest so long as the functions are normal. You may be surprised at my making such commonplace remarks, but the fact is that among doctors experimental proof is very often looked upon as the one decisive argument. Because there are doses so small that they have no influence whatever on the auriculo-ventricular conduction, or on the ventricular complex of the electro-cardiogram, it is thought unwise to give such doses to a patient. However, there is available clear clinical experimental proof of the beneficial action of very small doses, and, as I have said repeatedly, this puts us under the obligation of not omitting this safe clinical experiment in suitable cases. I call a daily dose of 5 centigrams or less of the powdered leaves a very small dose.

I remember how, some twenty-five years ago, I had my first opportunity of demonstrating the benefit of it before a large audience, the patient being a very popular and well-known man in his country. He was 73 years old, and had slipped into one of those very precarious states between the Scylla of suffocation by lung stasis and the Charybdis of painful liver swelling and oedema. The larger doses of digitalis were not tolerated by the stomach, and the doctors refused to give it any further chance. Seeing the absolute necessity of at least some digitalis, I advised that they give the patient 4 centigrams of the leaves daily, which by the attendant older doctors was deemed ridiculous. I insisted on giving the dose a fair trial, and after a few weeks it proved a great success. Of course, there could not be any question of complete cure, but the patient felt much better and was grateful, finding that his respiration was better and the distressing nightly attacks of suffocation had disappeared. The diuresis improved and the somewhat stormy swellings of the liver subsided. At that time this success was not new to me, and since then very often such small doses have had a marked visible effect. Recently I have been changing this sort of treatment for another form, with regard to which a few words should be spoken now.

2. *Treatment with Larger Doses.*

Every physician's experience shows that in the treatment of the great majority of serious cases of heart failure there comes a moment at which further progress seems, and really is, impossible. Whatever may have been our first success, we cannot remove the valvular defects or the anatomical lesions of the heart muscle, nor can we prevent further narrowing of the mitral or aortic valves. The beginning was wonderful; the pulse became slower, even regular, the heart became smaller and stronger, the urinary secretion was abundant, the liver, which had been distended to an unbearable extent, diminished in size, dyspnoea was lost, and that greatest blessing to the sufferer—sleep, the friend of mankind—returned to the patient without the need of any more morphine and hypnotics. But improvement stopped at a certain point, and further treatment seemed to have become useless. Very often it is the digitalis itself which, by its cumulative toxic action, makes continued administration impossible. We stop the drug, which now is abhorred by the patient, and after only a few days we see that part of our gain is lost; the body weight increases, the liver becomes more bulging again, and it grows clear to us that without digitalis we shall not be able to keep the patient in his individual optimal condition. After a few days of renewed digitalis treatment this same sequence of events recurs, and at the end the doctor sees that this intermittent digitalis treatment imposes upon him the very unsatisfactory task of trying to recover again and again what had been lost as soon as the digitalis was omitted for a period of some length. As every physician knows, the repeated very small dose is of no value here, and cannot help us any more.

It was clear, however, that some change in this form of intermittent digitalis treatment might be devised, and in the course of time I evolved a method which might be called the "every second day scheme." I gradually shortened the intervals in this treatment to the smallest extent—that is, to one day only; the interval might occur every second, third, or fourth day. It proved possible to continue full daily doses of 3 or 2 decigrams of the leaves as soon as such intervals occurred. This may be explained from the fact that a sufficiently large dose works at least during the next day; at the same time accumulation is prevented by the fact that on the following day the drug has left the organism.

There is no better case for studying the effects of this treatment than that of auricular fibrillation without serious muscular damage, and in which defibrillation by large doses of quinidine is not yet possible. The action of the drug and the improvement of the heart may be exactly measured from the decrease of ventricular rate and of the pulse deficit. By our first offensive of large daily doses we reduce in a few days a rate of, let us say, 150 to 170 per minute to one of something like 100 to 120. This means already a great improvement in the general condition of the patient. Our aim must now be to bring the ventricles down to a rate of 80 to 90, perhaps less, and to stabilize their activity at this level. We may do this without giving

rise to stomach trouble, not by reducing the original daily dose, but by introducing after every two days, later every second day, a free day—that is, a day without digitalis.

Of course, regular observation of the patient must determine which scheme we adopt in each individual case. Once we reach a frequency of 80 in the recumbent position it may be wise to reduce the daily dose from, let us say, 3 decigrams to 2, but not less. With further improvement we may even find it possible to give the full dose every third day only; and, curious to say, this method allows us to keep the patient and his heart continuously under a fully active dose of digitalis without any signs of intoxication. This treatment may be continued for an indefinite number of relatively healthy years.

Clinical experimental proof of the excellent success of this simple scheme is easily obtained in this category of patients. By carefully gauging the ventricular rate and the pulse deficit, and especially by making graphic records, it will be found that in regularly living patients both values are lower on the free days than on the days of digitalis administration. It is quite clear that the dose works most actively on the second day. If the patient is well you can introduce a second free day, and find out by counting the pulse whether digitalis action is still operative. This objective evidence will give the decision of how long intervals may be allowed. The same very simple tactics may have the same beneficial effect in treating other forms of heart trouble which require continuous digitalis treatment.

The only real difficulty to overcome is the opposition of the doctor, who has been taught, and found out for himself, that digitalis treatment should not be pushed for too long a period. In such cases it is the doctor who has to be treated, and his opposition may be overcome by making it clear that although this may involve treatment continued for years, as a matter of fact it is really intermittent treatment, which differs from the routine methods only in respect of shortness of the intermittences.

There are two important advantages in this scheme. First, the free days can be used for carrying out another treatment—for instance, with diuretics. The stomach is thus not overburdened by drugs, and we are assisted in this other treatment by the fact that it also is being prosecuted every second or third day. The other advantage is that after having stabilized the heart rate and having found out with what dosage this success was attained, we can send the patient home and tell the doctor, and even the patient, that the treatment should be continued until the next visit of the patient, and that the daily dose should never be altered, but longer intervals should be introduced when the pulse becomes too slow. On the other hand, the intervals should be shortened or the drug be given day by day continuously if signs of a worse condition begin to appear.

Ladies and gentlemen, it would have been very pleasant, at least to me, to illustrate what I have said with the histories of a great number of convincing cases. But this would be completely out of place, and every physician has the means to provide himself with proof at the bedside. On the other hand, I must be prepared to hear that I have not brought any news to you, but only that which you all knew and did already. In this case I can only state that what I have been saying is concordant, even almost identical, with the conclusions William Withering gave us out of his own experience. At any rate, I am in the very best company.

Perhaps one word more may be added. I wish to impress again upon my audience, particularly upon the students present, that I do not despise scientific research in the field of medicine. On the contrary, anyone who has watched my work must know that I have dived deeply into pure biology to get to an understanding of the intimate nature of certain clinical phenomena. But, as I said, medicine has two faces, and asks for two sorts of faithful servants: the pure scientist, and he who is solely the practitioner. You need not leave your own country to find the most wonderful examples. There is William Harvey, the thinker and the first experimenter, the author of *De Motu Cordis*, the tercentenary of the publication of which was celebrated less than two years ago; there is also William Withering, whose digitalis work was purely clinical, and whose name is now celebrated here, where he worked out his problems. Let us try to follow both of these men, to the benefit of mankind; but be pure and careful scientists in all your theoretical work, and whole-hearted physicians at the bedside. To the physician I say, never forget Withering, who, knowing nothing at all about the intimate action of digitalis on the heart, nevertheless gave the profession a work of undying value in his account of the foxglove.

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An Address
ON
CHOLECYSTITIS AND GALL-STONES.*

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CHOLECYSTITIS due to infection of the gall-bladder is one of the commonest of abdominal affections. In the course of time it often leads to the formation of gall-stones, from which about 10 per cent. of the population suffer. The causes of gall-stones may be considered under three headings.

(A) *Infection.*

This may be derived from any septic source anywhere in the body. The most important sources are the mouth, nose, throat, intestines, and especially the appendix. The most common organisms found in the walls of the gall-bladder are the streptococcus and the *Bacillus coli*; the staphylococcus, pneumococcus, *Bacillus pyocyaneus*, *Bacillus welchii*, and *Bacillus typhosus* are also sometimes discovered in the walls or contents of the gall-bladder.

1. The organisms may reach the gall-bladder through the blood, either by the cystic artery direct to the gall-bladder, or through the portal vein to the liver. The former is probably the most common, and carries organisms from distant parts, such as the mouth and throat, whereas the portal vein carries infection from the intestines. The organisms are then excreted by the liver into the bile, and thus reach the gall-bladder. *B. coli communis* infection of the urinary organs is very common in women, especially during pregnancy and after labour. This condition is frequently associated with cholecystitis, probably due to vascular spread of the infection.

2. The infection may spread through the *lymphatics*, especially from the liver, pancreas, or appendix.

3. It may invade the gall-bladder directly from any *inflamed organ* in contact with or adherent to it, such as an inflamed appendix or duodenal ulcer.

4. Infection may spread up from the duodenum along the *bile ducts*, especially if there is achlorhydria, as there is in about 40 per cent. of gall-stones. The absence of free hydrochloric acid allows the *Bacillus coli* to flourish in the duodenum.

It is very doubtful if gall-stones ever form in the absence of infection, which generally lurks deeply in the walls of the gall-bladder; but it is commonly believed that the single cholesterin stone forms in an aseptic gall-bladder, for there may be little sign of inflammation. It is probable, however, that the inflammation which may cause the stone to form subsequently disappears.

The stones generally form round a nucleus made of agglutinated bacteria, precipitated mucus, or debris from the epithelial walls, and above all from broken off papillae, perhaps laden with cholesterol. The crystalline deposits of cholesterin, calcium salts, or pigment are held together by an organic matrix derived from the inflamed gall-bladder.

(B) *Cholesteraemia.*

An excess of cholesterol in the blood may be due to obesity, pregnancy, menstruation, or a diet too rich in

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